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Genetic predisposition to obesity and lifestyle factors – the combined analyses of twenty-six known BMI- and fourteen known waist:hip ratio (WHR)-associated variants in the Finnish Diabetes Prevention Study

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Abstract

Recent genome-wide association studies have identified multiple loci associated with BMI or the waist:hip ratio (WHR). However, evidence on gene–lifestyle interactions is still scarce, and investigation of the effects of well-documented dietary and other lifestyle data is warranted to assess whether genetic risk can be modified by lifestyle. We assessed whether previously established BMI and WHR genetic variants associate with obesity and weight change in the Finnish Diabetes Prevention Study, and whether the associations are modified by dietary factors or physical activity. Individuals (n 459) completed a 3 d food record and were genotyped for twenty-six BMI- and fourteen WHR-related variants. The effects of the variants individually and in combination were investigated in relation to obesity and to 1- and 3-year weight change by calculating genetic risk scores (GRS). The GRS were separately calculated for BMI and the WHR by summing the increasing alleles weighted by their published effect sizes. At baseline, the GRS were not associated with total intakes of energy, macronutrients or fibre. The mean 1- and 3-year weight changes were not affected by the BMI or WHR GRS. During the 3-year follow-up, a trend for higher BMI by the GRS was detected especially in those who reported a diet low in fibre (P for interaction=0·065). Based on the present findings, it appears unlikely that obesity-predisposing variants substantially modify the effect of lifestyle modification on the success of weight reduction in the long term. In addition, these findings suggest that the association between the BMI-related genetic variants and obesity could be modulated by the diet.

Key words: **Obesity: Genetics: Polymorphisms: Lifestyles: Diets: Interactions: Interventions**

The growing burden of obesity is primarily related to environmental changes occurring over the last decades. However, not all people are affected equally by the deleterious effects of the obesogenic environment, whereas others carry genetic variants rendering them particularly sensitive to it[1]. The genetic understanding of common obesity has increased during recent years. The fat mass- and obesity-associated (*FTO*) gene identified in 2007 was the first locus unequivocally associated with BMI, and, to date, large-scale genome-wide association studies have identified more than fifty genetic loci to be robustly associated with obesity-related traits[2–9]. Interestingly, the genetic regulation of body fat distribution apparently involves loci that are largely distinct from those that influence BMI[9]. The effect sizes of the established loci are rather small. Only a few studies have investigated how the combined loci contribute to obesity risk and whether these loci can be

Abbreviations: DPS, Diabetes Prevention Study; *FTO*, fat mass- and obesity-associated gene; GRS, genetic risk scores; WHR, waist:hip ratio.

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used to improve the prediction of obesity or how these genes interact with different environmental exposures. The prospective study design provides an ideal approach to investigate the gene–environment hypothesis that a healthy diet can (partially) overcome genetic susceptibility to obesity.

In the present study, we investigated the effects of twenty-six BMI and fourteen waist:hip ratio (WHR) susceptibility variants on obesity and on 1- and 3-year weight change in the Finnish Diabetes Prevention Study (DPS). In addition, we investigated whether dietary intake and physical activity could modulate genetic effects on obesity. The effects of the variants were studied individually and in combination by calculating a genetic risk score (GRS).

Subjects and methods

Study population

The Finnish DPS was a clinical trial with five participating centres in Finland. Details of the DPS study design, methods and procedures have been published[10–12]. The main aim of the DPS was to assess the efficacy of an intensive diet and exercise programme to prevent or delay the onset of type 2 diabetes among high-risk individuals with impaired glucose tolerance. The main inclusion criteria were BMI over 25 kg/m^2 and age from 40 to 64 years. A total of 522 subjects were randomly assigned to an intensive diet and exercise counselling (n 265) or to a control (n 257) group. There were no differences at baseline in laboratory or anthropometric characteristics between the randomisation groups. The main goals of the intervention group were weight reduction ≥ 5 %, moderate intensity physical activity ≥ 30 min/d, dietary fat < 30 % of total energy, saturated fat < 10 % of total energy and fibre ≥ 15 g/4184 kJ (≥ 15 g/1000 kcal). To estimate how successfully these goals were achieved, each intervention goal was graded (0 = not achieved, 1 = achieved) at the 1-year follow-up and the 'success score' from 0 to 5 was computed as the sum of the grades[13]. Success in achieving the intervention goals was estimated from food records and exercise questionnaires collected at the 1-year examination.

Table 1. BMI and waist:hip ratio related single nucleotide polymorphisms (SNPs) that were genotyped

	Genes	SNP	Definition
BMI			
1	*NEGR1*	rs2815752	Neuronal growth regulator 1
2	*TNNI3K*	rs1514175	TNNI3 interacting kinase
3	*SEC16B*	rs543874	SEC16 homologue B (*Saccharomyces cerevisiae*)
4	*TMEM18*	rs2867125	Transmembrane protein 18
5	*FANCL*	rs887912	Fanconi anaemia, complementation group L
6	*CADM2*	rs13078807	Cell adhesion molecule 2
7	*ETV5*	rs9816226	Ets variant gene 5
8	*GNPDA2*	rs10938397	Glucosamine-6-phosphate deaminase 2
9	*SLC39A8*	rs13107325	Solute carrier family 39 (Zn transporter), member 8
10	*FLJ35779*	rs2112347	POC5 centriolar protein homologue
11	*NUDT3*	rs206936	Nudix (nucleoside diphosphate-linked moiety X)-type motif 3
12	*TFAP2B*	rs987237	Transcription factor AP-2β (activating enhancer binding protein 2β)
13	*LRRN6C*	rs10968576	Leucine-rich repeat neuronal 6C family
14	*RPL27A*	rs4929949	Ribosomal protein L27A
15	*BDNF*	rs10767664	Brain-derived neurotrophic factor
16	*MTCH2*	rs3817334	Mitochondrial carrier 2
17	*FAIM2*	rs7138803	Fas apoptotic inhibitory molecule 2
18	*PRKD1*	rs11847697	Protein kinase D1
19	*MAP2K5*	rs2241423	Mitogen-activated protein kinase kinase 5
20	*GPRC5B*	rs12444979	G protein-coupled receptor, family C, group 5, member B
21	*SH2B1*	rs7359397	SH2B adaptor protein 1
22	*FTO*	rs1558902	Fat mass and obesity associated
23	*MC4R*	rs571312	Melanocortin 4 receptor
24	*KCTD15*	rs29941	K channel tetramerisation domain containing 15
25	*QPCTL*	rs2287019	Glutaminyl-peptide cyclotransferase-like
26	*TMEM160*	rs3810291	Transmembrane protein 160
Waist:hip ratio			
1	*TBX15-WARS2*	rs984222	T-Box 15-tryptophanyl tRNA synthetase 2, mitochondrial
2	*GRB14*	rs10195252	Growth factor receptor-bound protein 14
3	*ADAMTS9*	rs6795735	A disintegrin-like and metallopeptidase with thrombospondin type 1 motif, 9
4	*NISCH-STAB1*	rs6784615	Nischarin-stabilin-1
5	*LY89*	rs1294421	Paired-Ig-like receptor A1
6	*VEGFA*	rs6905288	Vascular endothelial growth factor A
7	*RSPO3*	rs9491696	R-spondin 3
8	*HOXC13*	rs1443512	Homeobox C13
9	*ZNRF3-KREMEN1*	rs4823006	Zn and ring finger 3-kringle containing transmembrane protein 1
10	*DNM3-PIGC*	rs1011731	Dynamin 3-phosphatidylinositol glycan anchor biosynthesis, class C
11	*LYPLAL1*	rs4846567	Lysophospholipase-like 1
12	*CPEB4*	rs6861681	Cytoplasmic polyadenylation element binding protein 4
13	*NFE2L3*	rs1055144	Nuclear factor (erythroid-derived 2)-like 3
14	*ITPR2-SSPN*	rs718314	Inositol 1,4,5-trisphosphate receptor, type 2-sarcospan

The most intensive intervention was carried out during the first year of the study, and the study was terminated after a mean follow-up of 3·2 years at which time the risk of diabetes had been reduced by 58 % in the intervention group compared with the control group[11,12]. In the present study, the baseline, 1-year and 3-year data were examined. Anthropometric measurements were performed at baseline and at the annual visits. The present study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving study participants were approved by the Ethics Committee of the National Public Health Institute in Helsinki. All participants volunteered for the study and gave their written informed consent.

Anthropometric measurements

Detailed methodologies for all measurements performed in the DPS have been described previously[10]. Weight and height were measured in light clothing, and BMI was calculated as weight (kg)/height (m^2). Waist circumference was measured midway between the lowest rib and the iliac crest, and hip circumference over the great trochanters. The WHR was then calculated.

Assessment of dietary intake and physical activity

The study participants completed a 3 d food record at baseline and before each annual study visit[12,14]. They were asked to write down everything they ate and drank using a picture booklet of portion sizes of typical foods as the reference. The completeness of the food records was checked at a session with the study nutritionist during the study visit. Nutrient intake was calculated with a dietary analysis program developed at the National Public Health Institute[15]. In the present study, the average/median intakes at baseline and at the 1-, 2- and 3-year follow-ups were used in the statistical analyses. The number of the available food records was 453, 447, 421 and 382, respectively.

Physical activity was assessed at baseline by the validated Kuopio Ischaemic heart disease Risk Factor Study 12-month Leisure-Time Physical Activity questionnaire[16]. The questionnaire provides detailed quantitative information on the duration, frequency and mean intensity of the most common lifestyle and structured leisure-time physical activity as recalled over the previous 12 months.

Genotyping

Genotypes of forty SNPs (Table 1), comprising twenty-six risk SNPs for BMI and fourteen risk SNPs for WHR, were obtained by genotyping the Metabochip[17], a custom Illumina© iSelect array which assays approximately 200 000 SNPs identified through genome-wide meta-analyses for metabolic and atherosclerotic/CVD and traits.

Of the 522 study subjects in the Finnish DPS, 479 gave permission for the genetic analysis, and were genotyped for the Metabochip. After genotyping, twenty individuals with missing genotype data (one SNP or more) were excluded, resulting in a total of 459 study subjects (153 men and 306 women).

Table 2. Basic characteristics of the Finnish Diabetes Prevention Study participants at baseline

(Mean values and standard deviations)

	Mean	SD
Sex (*n*)		
Male	153	
Female	306	
Age (years)	55·2	7·0
Weight (kg)	86·5	14·2
BMI (kg/m^2)	31·3	4·5
Waist circumference (cm)	101·5	10·9
Hip circumference (cm)	110·1	10·2
Waist:hip ratio	0·93	0·07
Total energy		
kcal/d	1773	518
kJ/d	7418	2167
Protein (E%)	17·6	3·4
Fat (E%)	36·7	6·5
SFA (E%)	16·7	4·1
MUFA (E%)	13·0	2·8
PUFA (E%)	5·8	1·9
Carbohydrates (E%)	43·2	6·9
Fibre (g)	19·9	7·4
Leisure-time physical activity, >3·5 MET-h/week	2·7	3·2
BMI-increasing allele		
Median	26	
Range	14–34	
Weighted sum of BMI-increasing alleles	3·7	0·5
WHR-increasing alleles		
Median	15	
Range	7–21	
Weighted sum of WHR-increasing alleles	0·5	0·1

E%, percentage of energy; MET, metabolic equivalents; WHR, waist:hip ratio.

Statistical analyses

Statistical analyses were performed using the IBM SPSS Statistics for Windows 19.0 (SPSS, Inc.). Data are presented as means and standard deviations. $P < 0{\cdot}05$ was considered as statistically significant. Normality of variable distributions was tested with the Kolmogorov–Smirnov test or by plotting the residuals of each statistical test. Logarithmic transformation was successfully used to improve normality when necessary.

Genotypes were coded 0, 1 or 2 according to the number of published BMI/WHR-increasing alleles (resulting in a score ranging from 0 to 52 for BMI and 0 to 28 for WHR). The BMI/WHR-increasing alleles were weighted by their effect sizes published earlier (Tables 2 and 3) [7,9]. The GRS was created by summing the number of BMI- or WHR-increasing alleles weighted by their effect size to estimate the total BMI- or WHR-increasing effect. The GRS was included in the statistical models as a continuous score, and in the figures the GRS is illustrated as divided into tertiles.

Univariate general linear model analyses were used to study the effect of the genotypes (Tables 3 and 4) and GRS (Table 5) on obesity-related traits. The genetic associations were analysed assuming an additive genetic model. The mean 1-year weight change by the GRS and intervention success scores (Fig. 1(a) and (b)) was analysed by the univariate general linear model. In addition, a separate analysis for multiple linear regression was used to assess the influence of BMI/WHR-related SNP, age, sex and intervention on the variation of BMI or WHR change during the first year. Since in the first model including

Table 3. SNPs associated with BMI, published effect alleles, allele frequencies, published effect sizes, β and 95 % CI for per-allele associations with baseline BMI in the Finnish Diabetes Prevention Study (DPS)

(β Values, standard errors and 95 % confidence intervals)

				Published (per-allele change in BMI)		DPS			
Nearest gene*	SNP	Published effect allele/other†	Published effect allele frequency†	β	SEM	DPS effect allele frequency	β	95 % CI	P‡
NEGR1	rs2815752	A/G	0·61	0·13	0·02	0·67	0·103	−0·542, 0·748	0·723
TNNI3K	rs1514175	A/G	0·43	0·07	0·02	0·48	−0·272	−0·855, 0·312	0·354
SEC16B	rs543874	G/A	0·19	0·22	0·03	0·18	−0·112	−0·904, 0·681	0·641
TMEM18	rs2867125	C/T	0·83	0·31	0·03	0·84	0·274	−0·513, 1·061	0·415
FANCL	rs887912	T/C	0·29	0·10	0·02	0·28	−0·044	−0·671, 0·583	0·931
CADM2	rs13078807	G/A	0·20	0·10	0·02	0·18	−0·042	−0·803, 0·719	0·831
ETV5	rs9816226	T/A	0·82	0·14	0·03	0·83	−0·120	−0·900, 0·660	0·789
GNPDA2	rs10938397	G/A	0·43	0·18	0·02	0·48	0·939	−0·556, 0·601	0·966
SLC39A8	rs13107325	T/C	0·07	0·19	0·04	0·01	−0·981	−3·494, 1·532	0·521
FLJ35779	rs2112347	T/G	0·63	0·10	0·02	0·59	0·215	−0·367, 0·797	0·548
NUDT3	rs206936	G/A	0·21	0·06	0·02	0·21	−0·153	−0·900, 0·594	0·690
TFAP2B	rs987237	G/A	0·18	0·13	0·03	0·23	0·181	−0·512, 0·873	0·510
LRRN6C	rs10968576	G/A	0·31	0·11	0·02	0·41	0·000	−0·586, 0·585	0·966
RPL27A	rs4929949	C/T	0·52	0·06	0·02	0·52	0·745	0·165, 1·326	0·013
BDNF	rs10767664	A/T	0·78	0·19	0·03	0·84	1·096	0·239, 1·953	0·019
MTCH2	rs3817334	T/C	0·41	0·06	0·02	0·37	0·306	−0·304, 0·916	0·324
FAIM2	rs7138803	A/G	0·38	0·12	0·02	0·41	−0·074	−0·665, 0·517	0·856
PRKD1	rs11847697	T/C	0·04	0·17	0·05	0·02	1·144	−1·200, 3·488	0·482
MAP2K5	rs2241423	G/A	0·78	0·13	0·02	0·85	0·222	−0·608, 1·053	0·719
GPRC5B	rs12444979	C/T	0·87	0·17	0·03	0·86	0·170	−0·669, 1·009	0·687
SH2B1	rs7359397	T/C	0·40	0·15	0·02	0·41	−0·122	−0·708, 0·465	0·705
FTO	rs1558902	A/T	0·42	0·39	0·02	0·44	0·912	0·330, 1·495	0·002
MC4R	rs571312	A/C	0·24	0·23	0·03	0·19	0·006	−0·777, 0·789	0·993
KCTD15	rs29941	G/A	0·67	0·06	0·02	0·61	−0·383	−0·965, 0·199	0·177
QPCTL	rs2287019	C/T	0·80	0·15	0·03	0·77	0·409	−0·297, 1·115	0·229
TMEM160	rs3810291	A/G	0·67	0·09	0·02	0·64	−0·350	−0·951, 0·252	0·238

* For definition of genes see Table 1.
† Speliotes *et al.*[7].
‡ Univariate general linear model, unadjusted for ln-transformed values.

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Table 4. SNPs associated with waist:hip ratio (WHR), published effect alleles, allele frequencies, published effect sizes, β and 95 % CI for per-allele associations with baseline WHR in the Finnish Diabetes Prevention Study (DPS)
(β Values, standard errors and 95 % confidence intervals)

Nearest gene*	SNP	Published effect allele/other†	Published effect allele frequency †	Published (per change of WHR-increasing allele)		DPS		
				β	SEM	β	95 % CI	P ‡
TBX15-WARS2	rs984222	G/C	0·37	0·034	0·71	0·001	−0·010, 0·011	0·942
GRB14	rs10195252	T/C	0·60	0·033	0·34	0·006	−0·004, 0·016	0·206
ADAMTS9	rs6795735	C/T	0·41	0·025	0·64	−0·003	−0·013, 0·006	0·476
NISCH-STAB1	rs6784615	T/C	0·94	0·043	0·96	−0·019	−0·042, 0·004	0·100
LY89	rs1294421	G/T	0·39	0·028	0·61	0·002	−0·007, 0·012	0·634
VEGFA	rs6905288	A/G	0·56	0·036	0·60	0·001	−0·009, 0·010	0·932
RSPO3	rs9491696	G/C	0·52	0·042	0·51	−0·004	−0·014, 0·006	0·428
HOXC13	rs1443512	A/C	0·24	0·031	0·29	0·002	−0·009, 0·013	0·752
ZNRF3-KREMEN1	rs4823006	A/G	0·57	0·023	0·56	0·010	0·001, 0·020	0·038
DNM3-PIGC	rs1011731	G/A	0·57	0·028	0·44	0·004	−0·005, 0·013	0·403
LYPLAL1	rs4846567	G/T	0·28	0·034	0·72	−0·006	−0·017, 0·004	0·229
CPEB4	rs6861681	A/G	0·34	0·022	0·41	0·007	−0·003, 0·017	0·145
NFE2L3	rs1055144	T/C	0·21	0·040	0·27	0·010	−0·001, 0·021	0·072
ITPR2-SSPN	rs718314	G/A	0·74	0·030	0·28	0·002	−0·009, 0·013	0·692

*For definition of genes see Table 1.
†Heid *et al.*[9], β values combined (discovery + follow-up).
‡Univariate general linear model, unadjusted.

all variables, sex was a significant predictor, regression analyses were also performed separately by sex.

A linear mixed model was used to assess the mean 3-year weight change by the GRS (Fig. 2 and Fig. S1 (available online)).

Results

BMI- and waist:hip ratio-associated SNPs at baseline

The summary of the basic characteristics of the Finnish DPS participants at baseline are presented in Table 2. All genetic markers were consistent with Hardy–Weinberg equilibrium ($P > 0{\cdot}0001$). The BMI-associated SNPs, published effect sizes, allele frequencies and associations with baseline BMI are presented in Table 3. At baseline, *FTO* ($P = 0{\cdot}002$) associated with BMI and the differences in BMI by the *FTO* genotype have been reported previously in detail[18]. Furthermore, as a novel finding in the present study population, SNPs in or near *RPL27A* ($P = 0{\cdot}013$) and *BDNF* ($P = 0{\cdot}019$) demonstrated a nominal association with BMI.

The WHR-associated SNPs, published effect sizes, allele frequencies and associations with baseline WHR are presented in Table 4. *ZNRF3-KREMEN1* was associated with WHR ($P = 0{\cdot}038$).

Genetic risk score at baseline

The associations between BMI- and WHR-related GRS (weighted on effect sizes) and weight, BMI, waist circumference, WHR, leisure-time physical activity and dietary intake at baseline are presented in Table 5. BMI GRS were associated significantly with BMI and waist circumference ($P = 0{\cdot}006$ for both). WHR GRS did not show associations with any of these variables.

1-Year follow-up analyses

Of the individual BMI- and WHR-associated SNP, *NUDT3* showed an association with the 1-year BMI change ($\beta = -0{\cdot}302$ (95 % CI −0·584, −0·019), $P = 0{\cdot}036$). *LYPLAL1* ($\beta = 0{\cdot}007$ (95 % CI 0·002, 0·013), $P = 0{\cdot}012$), *NFE2L3* ($\beta = -0{\cdot}007$ (95 % CI −0·013, −0·002), $P = 0{\cdot}013$) and *CPEB4* ($\beta = -0{\cdot}006$ (95 % CI −0·011, −0·001), $P = 0{\cdot}020$) were associated with the 1-year waist change.

The results of the mean 1-year weight loss by the GRS (created of BMI-related SNPs) are presented in Fig. 1(a) for the intervention and in Fig. 1(b) for the control group. The mean weight loss is illustrated in the entire groups and as divided by a success score as the sum of the achieved intervention goals. In both groups, there were no significant GRS × success score interactions and the mean weight loss was similar in all GRS groups. There were no significant interactions or differences between the GRS groups created of WHR-related SNPs either (data now shown).

In the linear multiple regression analyses including all variables (BMI-associated SNPs, age, sex and intervention), only intervention ($P < 0{\cdot}001$) and sex ($P = 0{\cdot}039$) explained significantly part of the variance of BMI during the first year.

Table 5. Associations between BMI- and waist:hip ratio (WHR)-related genetic risk scores (weighted on effect sizes) and weight, BMI, waist circumference, WHR, leisure-time physical activity and dietary intake at baseline
(β Values and 95 % confidence intervals)

	BMI GRS			WHR GRS		
	β	95 % CI	P*	β	95 % CI	P*
Weight (kg)	2·572	−0·106, 5·251	0·060	5·023	−12·210, 22·256	0·567
BMI (kg/m^2)	1·183	0·331, 2·036	0·006†	0·990	−4·517, 6·497	0·742†
Waist circumference (cm)	2·905	0·854, 4·956	0·006	3·997	−9·279, 17·273	0·554
WHR	0·012	−0·002, 0·026	0·084	0·053	−0·036, 0·142	0·241
Leisure-time physical activity, >3·5 MET-h/week	0·088	−0·535, 0·710	0·782	−0·891	−4·805, 3·023	0·655
Total energy			0·742			0·536
kcal/d	16·413	−81·587, 114·412		−197·876	−825·298, 429·545	
kJ/d	68·7	−341·4, 478·7		−827·9	−3453·0, 1797·2	
Fat (E%)	0·659	−0·564, 1·882	0·290	4·501	−3·329, 12·331	0·259
SFA (E%)	0·324	−0·450, 1·097	0·411	4·584	−0·354, 9·521	0·069
MUFA (E%)	−0·069	−0·598, 0·461	0·799	0·495	−2·897, 3·887	0·774
PUFA (E%)	0·037	−0·330, 0·404	0·844	−0·826	−3·176, 1·523	0·490
Carbohydrates (E%)	−0·598	−1·903, 0·706	0·368	0·109	−8·254, 8·472	0·980
Fibre (g)	0·634	−0·761, 2·028	0·372	−5·040	−13·967, 3·887	0·268

GRS, genetic risk scores; MET, metabolic equivalents; E%, percentage of energy.
* Univariate general linear model, unadjusted.
† ln-transformed.

In the sex-specific analyses, the intervention remained a significant ($P < 0·001$) predictor for BMI change for both sexes. In addition, *RPL27A* rs4929949 ($P = 0·023$) and *BDNF* rs10767664 ($P = 0·036$) were significantly associated with a variation in BMI change in men.

In the corresponding analysis for the change in the WHR, intervention ($P = 0·045$), age ($P = 0·014$) *LYPLAL1* rs4846567 ($P = 0·010$), *CPEB4* rs6861681 ($P = 0·034$) and *NFE2L3* rs1055144 ($P = 0·015$) were associated with the WHR during the first year.

3-Year follow-up analyses

The mean BMI during the 3-year follow-up in each GRS (created of BMI-related SNPs) group is illustrated in Fig. S1(a) (available online) for the intervention group and in Fig. S1(b) (available online) for the control group. There were no differences between the GRS groups. Changes in the WHR during the 3- year follow-up between the GRS groups (created of WHR-related SNPs) did not differ either (data not shown).

When the median dietary intake was examined in relation to GRS and BMI during the 3-year follow-up, we observed a clear trend that individuals following a diet high in fibre did not differ in BMI between the GRS groups (P for interaction=0·065, adjusted for age, sex and randomisation group; Fig. 2(b)). Individuals who reported a diet low in fibre in the middle and highest BMI GRS tertile groups appeared to have a higher BMI than individuals in the lowest GRS group ($P = 0·051$). For carbohydrate intake (Fig. 2(a)), the interaction was not significant ($P = 0·775$). The corresponding interactions for fat, SFA and protein are illustrated in Fig. 2(c)–(e)). Of these analyses, only SFA intake seemed to modify the association between the GRS and BMI (P for interaction=0·004; Fig. 2(d)). There was no evidence that total energy intake would modify the association between the GRS and BMI (P for interaction=0·509; data not shown). There were no significant WHR–GRS interactions with any of the dietary factors (data not shown).

Discussion

Based on the present findings, it appears unlikely that the known obesity-predisposing variants modify the effect of lifestyle modification on the success of weight reduction. Furthermore, we provide novel long-term data on the modulation of the genetic risk of obesity by diet. These findings strengthen the view that obesity represents a complex multi-factorial disease resulting from the interaction of susceptibility genes with the diet. The main finding of the present study suggests that the association between the genetic variants and common obesity could be attenuated by a diet high in fibre.

Previous studies on variants in and near the *FTO* gene have provided evidence that the deleterious effects of obesity-predisposing polymorphisms can be suppressed by lifestyle factors, such as physical activity[19]. A cross-sectional study by Sonestedt *et al.*[20] showed that an increase in BMI across *FTO* genotype groups was restricted to those who reported a diet low in carbohydrate and high in fat. Moleres *et al.*[21] showed in children that *FTO* risk allele carriers consuming a diet high in saturated fat had an increased obesity risk. Corella *et al.*[22] similarly demonstrated that a high intake of saturated fat strengthens the association between *FTO* and BMI, but they did not find interactions with carbohydrate intake.

To our knowledge, the present study is the first to assess the interactions between dietary macronutrient composition and obesity-predisposing variants on a large scale (twenty-six BMI- and fourteen WHR-related variants) and in the long term. At baseline, GRS (created of BMI/WHR-related SNPs) did not associate with total intakes of energy, macronutrients or fibre. However, those who reported a diet low in fibre appeared to have a higher BMI by GRS (created of BMI-related SNPs). Dietary intake was divided by median, and there were

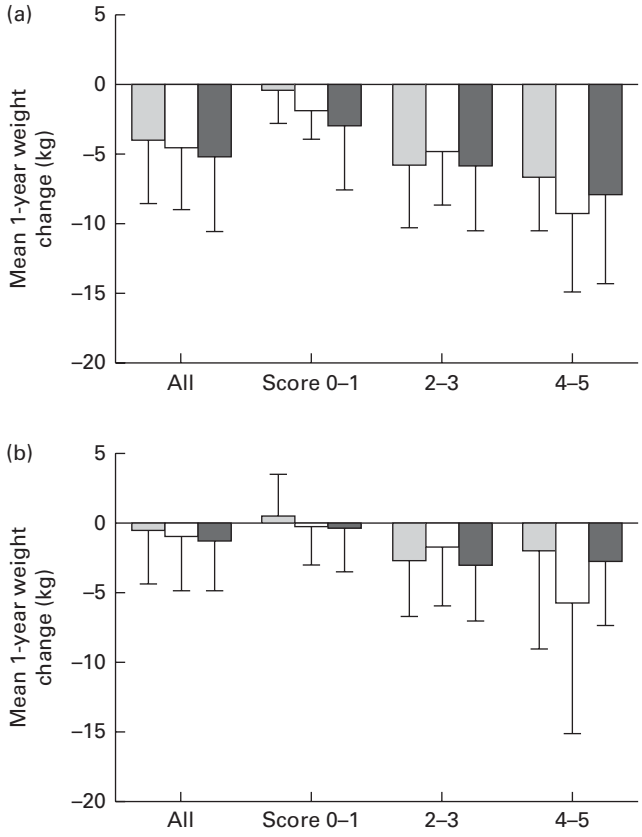

Fig. 1. (a) The mean 1-year weight change in (a) the intervention group and (b) the control group of the Finnish Diabetes Prevention Study (DPS) and by the genetic risk score (GRS) groups and by the achieved success scores. Scores 0–1, 2–3 and 4–5: *P* for interaction=(a) 0·176 and (b) 0·436. □, GRS, first tertile; □, GRS, second tertile; ■, GRS, third tertile.

no differences in BMI between the GRS groups among individuals who consumed >19 g/d from fibre (Fig. 2(b)). However, the differences in BMI by GRS tertile groups were more obvious among individuals consuming <19 g/d from fibre.

In general, a higher intake of whole grains is associated with a lower BMI in epidemiological studies[23], and the risk of obesity may be reduced by replacing refined cereal sources with whole-grain, high-fibre foods[24]. In the present study, a diet low in fibre appeared to have a BMI-increasing effect, particularly in those who carried large numbers of obesity-predisposing variants. Although it is known that various nutrients modulate gene expression and thus influence the impact of genetic variants[25], the mechanisms behind the present observation remain to be explained. Preliminary evidence for gene–diet interaction has come from studies on the *FTO* locus[19–21]. Furthermore, we recently reported a higher BMI by the *FTO* risk genotype in those who reported a diet low in carbohydrates and fibre[26]. In the present study, genetic predisposition was estimated by the multiple well-established obesity variants rather than a single locus.

We did not observe significant interactions between the GRS and physical activity in determining BMI at baseline. Several studies have reported that the effect of common *FTO* variants is attenuated in active individuals in different populations[19]. In addition, Li *et al.*[27] have shown that living a physically active lifestyle is associated with a 40 % reduction in genetic predisposition to common obesity, as estimated by the number of risk alleles carried for the twelve genome-wide association-identified loci. In the present study, a failure to detect an interaction with physical activity may reflect the influence of population-specific characteristics such as high overall physical activity levels in the study population[28] and a relatively small sample size.

At baseline, BMI/WHR GRS did not associate with total energy or macronutrient intake. Some, but not all, studies on *FTO* have demonstrated associations with increased energy intake or preference for energy-dense foods[29,30]. The present study suggests instead that obesity-predisposing variants may have a macronutrient-specific effect on BMI, and a fibre-rich diet also indicates less energy-dense food choices. In the present analyses, also SFA intake seemed to modify the association between the GRS and BMI, and the differences between the GRS groups were significant ($P = 0{\cdot}034$) in the low SFA intake group. The reason for this somewhat unanticipated finding remains unexplained.

BMI GRS were associated significantly with BMI and waist circumference at baseline. WHR GRS did not show associations with any of the obesity-related variables. Of the individual variants, only *FTO* rs9939609 was associated with baseline BMI, as reported previously in detail[18]. Furthermore, SNPs in or near *RPL27A* and *BDNF* demonstrated a nominal association with BMI at baseline. *NUDT3* showed a nominal association with the 1-year BMI change. Of the WHR-associated SNPs, *ZNRF3-KREMEN1* was associated with WHR, and *LYPLAL1*, *NFE2L3* and *CPEB4* were associated with the 1-year waist change. However, associations were statistically quite weak, and multiple comparisons would have attenuated the *P* values to a non-significant level. In the sex-specific linear multiple regression analyses including all BMI-associated SNPs, age and intervention, *RPL27A* rs4929949 and *BDNF* rs10767664 explained ($P=0{\cdot}023$ and $P = 0{\cdot}036$, respectively) part of the variance of BMI during the first year but only in men. However, we consider these associations as statistically quite weak and acknowledge the need for further evidence to confirm the associations particularly in the Finnish population. Furthermore, it should be noted that the intervention itself remained a highly significant ($P<0{\cdot}001$) predictor for the 1-year BMI change for both sexes.

Relatively weak associations between SNP and obesity may be due to the fact that these individuals were already overweight/obese, differing from the population from which the variants were originally identified[7,9]. Moreover, common genetic variants generally have only a modest effect, and the interaction of these variants with each other or with environmental factors is more important in determining the observed phenotype. Although it has been suggested that genetic testing has the potential to be a useful clinical or preventive tool when combined with appropriate information[31], the current focus should be on promoting a healthy environment.

GRS did not appear to modify weight reduction achieved by the lifestyle intervention. Weight development was also similar in all GRS groups divided by the achieved success scores: the

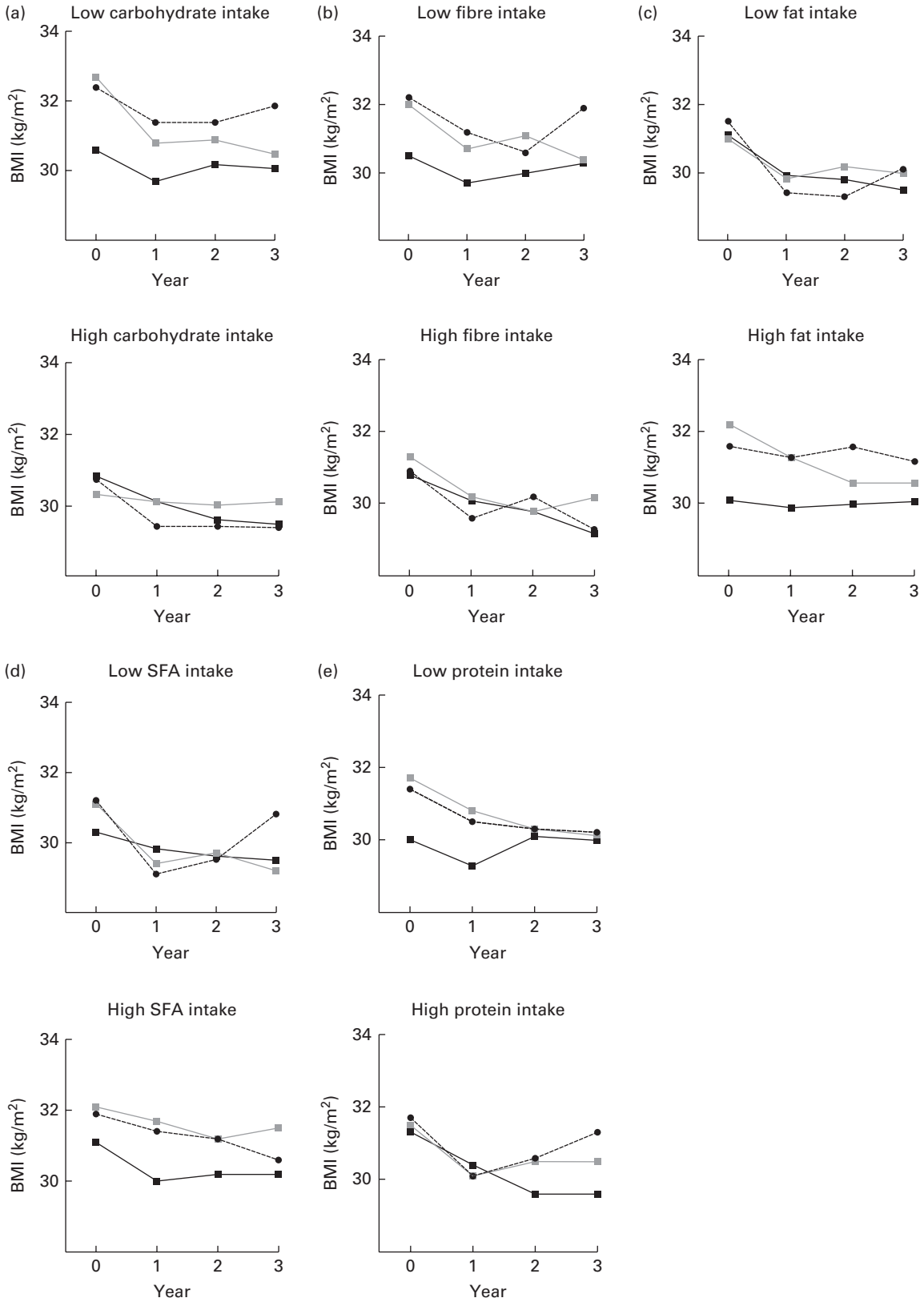

Fig. 2. BMI by (a) carbohydrate, (b) fibre, (c) fat, (d) SFA and (e) protein intake (low, high) and by BMI genetic risk score (GRS) during the 3-year follow-up. Analyses are adjusted for age, sex and randomisation group. The GRS was included as a continuous variable in the model. *P* for interaction=(a) 0·775, (b) 0·065, (c) 0·605, (d) 0·004 and (e) 0·479. (a) *P*=0·072 (low) and *P*=0·400 (high); (b) *P*=0·051 (low) and *P*=0·158 (high); (c) *P*=0·240 (low) and *P*=0·101 (high); (d) *P*=0·034 (low) and *P*=0·215 (high); (e) *P*=0·099 (low) and *P*=0·050 (high). –■–, GRS, first tertile; –■–, GRS, second tertile; –●–, GRS, third tertile.

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individuals who reached the intervention goals lost more weight regardless of the GRS group. Changes in BMI or WHR did not differ between the tertiles of GRS during the 3-year follow-up either. Thus, it appears to be unlikely that obesity-predisposing variants substantially modify the effect of lifestyle modification on the success of weight reduction in the long term. However, Delahanty *et al.*[32] recently tested the associations of sixteen obesity-predisposing variants with weight change in Diabetes Prevention Program participants. They found three SNPs (*NEGR1* rs2815752, *BDNF* rs6265 and *PPARG* rs1801282) that predicted weight regain, irrespective of the type of weight loss therapy, two of which (*BDNF* and *PPARG*) were robust to correction for multiple hypothesis testing. In the present study, *PPARG* was not included in the analyses; however, we have shown previously that the known Pro12Ala polymorphism of *PPARG2* modifies weight loss in the Finnish DPS participants[33]. Furthermore, in the present study, *BDNF* (rs10767664) demonstrated a nominal association with baseline BMI.

In the present study, the obese and prediabetic state of the study population may limit the generalisability of the results, and the obvious limitation is also a relatively modest sample size. Thus, we acknowledge the need for larger studies with varying environment to determine the exact nature of interactions. We did not adjust for multiple comparisons since the present study is a hypothesis-testing rather than hypothesis-generating study and is strongly based on already previously reported findings. The easiest method to correct for this problem would certainly be the Bonferroni according to the number of phenotypes and inheritance models. However, this method is very conservative and stringent. There is also a problem of a high correlation between the parameters tested and the repeated measurements. Furthermore, over-adjustment for multiple comparisons may increase type II error that reduces the power to detect significant differences. Reporting only genetic association studies with strongly positive results is also particularly susceptible to publication bias. However, we would like to emphasise that the strength of the DPS population is that it is carefully selected and clinically well characterised. Furthermore, habitual nutrient intakes of the study participants were annually estimated using 3 d food records, which is a reliable and high-quality method in analysing dietary intakes. It is also notable that the present study enables the investigation of long-term gene × environment interactions, and these kinds of data are seldom available.

In conclusion, based on the present findings, it appears unlikely that obesity-predisposing variants substantially modify the effect of lifestyle modification on the success of weight reduction in the long term. As a novel finding, we suggest that individuals who are genetically predisposed to obesity would benefit in the long term more from a diet high in fibre than individuals who are genetically protected.

Supplementary material

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/S0007114513001116

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References

1. Blakemore AI & Froguel P (2008) Is obesity our genetic legacy? *J Clin Endocrinol Metab* **93**, S51–S56.
2. Frayling TM, Timpson NJ, Weedon MN, *et al.* (2007) A common variant in the *FTO* gene is associated with body mass index and predisposes to childhood and adult obesity. *Science* **316**, 889–894.
3. Scuteri A, Sanna S, Chen WM, *et al.* (2007) Genome-wide association scan shows genetic variants in the *FTO* gene are associated with obesity-related traits. *PLoS Genet* **3**, e115.
4. Willer CJ, Speliotes EK, Loos RJ, *et al.* (2009) Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. *Nat Genet* **41**, 25–34.
5. Thorleifsson G, Walters GB, Gudbjartsson DF, *et al.* (2009) Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. *Nat Genet* **41**, 18–24.
6. Loos RJ, Lindgren CM, Li S, *et al.* (2008) Common variants near MC4R are associated with fat mass, weight and risk of obesity. *Nat Genet* **40**, 768–775.
7. Speliotes EK, Willer CJ, Berndt SI, *et al.* (2010) Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet* **42**, 937–948.
8. Meyre D, Delplanque J, Chèvre JC, *et al.* (2009) Genome-wide association study for early-onset and morbid adult obesity identifies three new risk loci in European populations. *Nat Genet* **41**, 157–159.
9. Heid IM, Jackson AU, Randall JC, *et al.* (2010) Meta-analysis identifies 13 new loci associated with waist–hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. *Nat Genet* **42**, 949–960.

10. Eriksson J, Lindström J, Valle T, *et al.* (1999) Prevention of type II diabetes in subjects with impaired glucose tolerance: the Diabetes Prevention Study (DPS) in Finland. Study design and 1-year interim report on the feasibility of the lifestyle intervention programme. *Diabetologia* **42**, 793–801.
11. Tuomilehto J, Lindström J, Eriksson JG, *et al.* (2001) Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* **344**, 1343–1350.
12. Lindström J, Louheranta A, Mannelin M, *et al.* (2003) The Finnish Diabetes Prevention Study (DPS): lifestyle intervention and 3-year results on diet and physical activity. *Diabetes Care* **26**, 3230–3236.
13. Lindström J, Peltonen M & Tuomilehto J (2005) Lifestyle strategies for weight control: experience from the Finnish Diabetes Prevention Study. *Proc Nutr Soc* **64**, 81–88.
14. Lindström J, Peltonen M, Eriksson JG, *et al.* (2006) High-fibre, low-fat diet predicts long-term weight loss and decreased type 2 diabetes risk: the Finnish Diabetes Prevention Study. *Diabetologia* **49**, 912–920.
15. Ovaskainen M-L, Valsta L & Lauronen J (1996) The compilation of food analysis values as a database for dietary studies – the Finnish experience. *Food Chem* **57**, 133–136.
16. Lakka TA & Salonen JT (1992) Intra-person variability of various physical activity assessments in the Kuopio Ischaemic Heart Disease Risk Factor Study. *Int J Epidemiol* **21**, 467–472.
17. Voight BF, Kang HM, Ding J, *et al.* (2012) The metabochip, a custom genotyping array for genetic studies of metabolic, cardiovascular, and anthropometric traits. *PLoS Genet* **8**, e1002793.
18. Lappalainen TJ, Tolppanen AM, Kolehmainen M, *et al.* (2009) The common variant in the *FTO* gene did not modify the effect of lifestyle changes on body weight: the Finnish Diabetes Prevention Study. *Obesity (Silver Spring)* **17**, 832–836.
19. Kilpeläinen TO, Qi L, Brage S, *et al.* (2011) Physical activity attenuates the influence of *FTO* variants on obesity risk: a meta-analysis of 218,166 adults and 19,268 children. *PLoS Med* **8**, e1001116.
20. Sonestedt E, Roos C, Gullberg B, *et al.* (2009) Fat and carbohydrate intake modify the association between genetic variation in the *FTO* genotype and obesity. *Am J Clin Nutr* **90**, 1418–1425.
21. Moleres A, Ochoa MC, Rendo-Urteaga T, *et al.* (2012) Dietary fatty acid distribution modifies obesity risk linked to the rs9939609 polymorphism of the fat mass and obesity-associated gene in a Spanish case–control study of children. *Br J Nutr* **107**, 533–538.
22. Corella D, Arnett DK, Tucker KL, *et al.* (2011) A high intake of saturated fatty acids strengthens the association between the fat mass and obesity-associated gene and BMI. *J Nutr* **141**, 2219–2225.
23. Giacco R, Della Pepa G, Luongo D, *et al.* (2011) Whole grain intake in relation to body weight: from epidemiological evidence to clinical trials. *Nutr Metab Cardiovasc Dis* **21**, 901–908.
24. Williams PG, Grafenauer SJ & O'Shea JE (2008) Cereal grains, legumes, and weight management: a comprehensive review of the scientific evidence. *Nutr Rev* **66**, 171–182.
25. Afman L & Müller M (2006) Nutrigenomics: from molecular nutrition to prevention of disease. *J Am Diet Assoc* **106**, 569–576.
26. Lappalainen T, Lindström J, Paananen J, *et al.* (2012) Association of the fat mass and obesity-associated (*FTO*) gene variant (rs9939609) with dietary intake in the Finnish Diabetes Prevention Study. *Br J Nutr* **108**, 1859–1865.
27. Li S, Zhao JH, Luan J, *et al.* (2010) Physical activity attenuates the genetic predisposition to obesity in 20,000 men and women from EPIC-Norfolk prospective population study. *PLoS Med* **7**, 1.
28. Jonsson A, Renström F, Lyssenko V, *et al.* (2009) Assessing the effect of interaction between an *FTO* variant (rs9939609) and physical activity on obesity in 15,925 Swedish and 2,511 Finnish adults. *Diabetologia* **52**, 1334–1338.
29. Cecil JE, Tavendale R, Watt P, *et al.* (2008) An obesity-associated *FTO* gene variant and increased energy intake in children. *N Engl J Med* **359**, 2558–2566.
30. Timpson NJ, Emmett PM, Frayling TM, *et al.* (2008) The fat mass- and obesity-associated locus and dietary intake in children. *Am J Clin Nutr* **88**, 971–978.
31. Meisel SF, Walker C & Wardle J (2011) Psychological responses to genetic testing for weight gain: A Vignette Study. *Obesity (Silver Spring)* **20**, 540–546.
32. Delahanty LM, Pan Q, Jablonski KA, *et al.* (2012) Genetic predictors of weight loss and weight regain after intensive lifestyle modification, metformin treatment, or standard care in the Diabetes Prevention Program. *Diabetes Care* **35**, 363–366.
33. Lindi VI, Uusitupa MI, Lindström J, *et al.* (2002) Association of the Pro12Ala polymorphism in the *PPAR-gamma2* gene with 3-year incidence of type 2 diabetes and body weight change in the Finnish Diabetes Prevention Study. *Diabetes* **51**, 2581–2586.